Intensive Care Med
https://doi.org/10.1007/s00134-023-07049-0

UNDERSTANDING THE DISEASE

Ten tips on fever

Marc Leone[1,2*], Nicole P. Juffermans[3,4] and Nathan D. Nielsen[5,6]

© 2023 Springer-Verlag GmbH Germany, part of Springer Nature

In critically ill patients, fever is a common symptom of disease, the pathophysiology of which is summarized in Fig. 1. Establishing the etiology in individual cases can be difficult, as can be determining an optimal management strategy. Efforts to control fever are probably excessive in many patients, inducing side-effects and potentially worsening outcomes. There likely is an optimum body temperature (BT), or BT range, for individual patients with specific conditions. Prior to initiating trials on fever control, an improved understanding of BT regulation during critical illness is warranted. Literature is quite limited, but here we provide 10 tips on fever, limited to adult non-neutropenic patients.

Be sure to measure temperature accurately

Body temperature (BT) has a core to skin gradient. Core BT most accurately reflects the temperature of internal organs. In critically ill patients, invasive monitoring provides the best estimate of the core BT. In a comparative study with pulmonary artery catheter measurements as referent, the smallest differences with pulmonary artery temperatures were found with readings taken from the esophagus, rectum, axilla, inguinal area, and urinary bladder [1]. Given impracticalities of pulmonary artery catheters, these results support the routine use of urinary bladder measurements whenever possible.

Remember: definitions of fever vary

Normal core BT is set at 37°C with physiologic variation between 0.5°C and 1°C. Guidelines propose a BT of ≥ 38.3°C as fever, though a lower threshold may be used in immunocompromised patients [2]. In diagnosing fever, environmental causes should be eliminated, and interventions like renal replacement therapy or drugs like ketamine that may interfere with BT considered as well. Overall, the rationale behind establishing a definition is to draw attention to patients at risk of infection.

Perform an extensive diagnostic workup in some, but not all, febrile patients

Fever often leads to a diagnostic workup that includes collecting samples and imaging to identify a source of suspected infection. In patients for whom initiation of empiric antibiotics is deemed appropriate, these steps are recommended [3]. However, an extensive workup is not useful in all febrile patients, e.g.: those with immediate postoperative fever that corresponds to the peak inflammatory response, while adding to costs and inappropriate treatment. In a cohort study of 100 patients with early postoperative fever, workup was useful in only 9% of cases. Fever evaluation should be protocolized so as to reduce low-yield workups [4].

Consider non-infectious causes for very high fever

Most infectious disorders usually do not cause a core BT > 38.9°C. However, rarely, core BT can exceed 41.1°C ("hyperpyrexia") during infection and may be deleterious, though optimal management in these circumstances remains unclear. As many of the causes of non-infectious hyperpyrexia require specific assessments and therapies and can have deadly consequences if not addressed properly, it is essential to consider non-infectious etiologies for temperature elevations of this severity. Entities such as serotonin syndrome, malignant hyperthermia, neuroleptic malignant syndrome, thyroid storm, heat stroke, acute hemolytic transfusion reactions and severe drug reactions fall into this category [5].

Actively treat malignant hyperthermia

Malignant hyperthermia, manifest by hypercapnia, muscle rigidity, arrythmias, and hyperthermia, may develop

*Correspondence: marc.leone@ap-hm.fr
[1] Department of anesthesiology and intensive care unit, North Hospital, Assistance Publique Hôpitaux, service d'anesthésie et de réanimation, hôpital Nord, Chemin des Bourrely, Universitaires de Marseille, Aix Marseille University, 13015 Marseille, France
Full author information is available at the end of the article

SHOUT
SHARE
IT

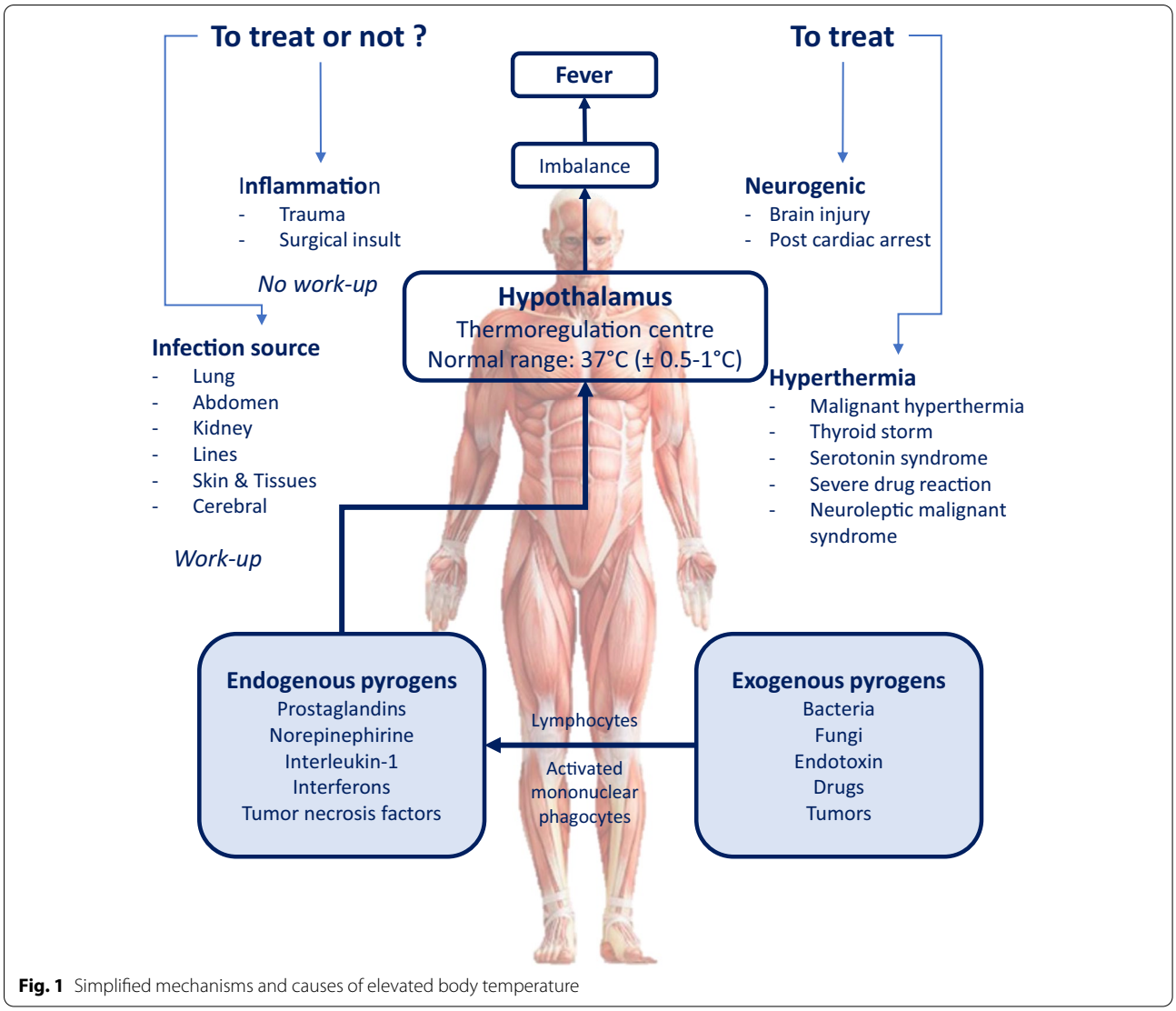

Fig. 1 Simplified mechanisms and causes of elevated body temperature

from exposure to an anesthetic triggering agent. The mechanism is related to impaired magnesium inhibition of sarcoplasmic reticulum calcium release and extracellular calcium entry. Broadly, management includes oxygen support, extracorporeal cooling, chilled intravenous fluids, sedation and specific drugs such as dantrolene [6].

Be careful with fever control in patients with sepsis

Very high BT is associated with mortality in sepsis, presumably due to increased metabolic demand. Animal studies suggest that lowering BT improves sepsis outcomes. However, a human sepsis trial showed that therapeutic hypothermia (32–34°C) actually worsened organ failure [7].

Fever control has generated conflicting results, with improved hemodynamics in one trial [7] but adverse effects in two other studies [8, 9]. Possibly, sepsis sub-populations may have differing responses to fever control.

Acetaminophen and cooling devices do not improve outcomes in febrile septic patients

Acetaminophen is often used in septic patients. Nevertheless, the evidence does not support this practice, as survival was similar in a trial in 700 febrile patients with suspected or proven sepsis randomized to acetaminophen or placebo [10]. In another study, patients in the acetaminophen group had a modest reduction in BT but a significant decrease in mean arterial pressure and heart rate [11]. Notwithstanding potential improvement in patient comfort, treatment of fever with acetaminophen is ineffective at altering risk of death and can worsen hemodynamics in sepsis. In addition, other harmful effects such as elevation of liver enzymes have

been reported [10, 11]. In contrast, cooling devices are effective at reducing BT, even in critically ill sepsis patients. A comparison of the different methods suggest that intravascular cooling and hydrogel cooling systems have higher efficacy than surface cooling devices [12]. However, in patients with fever due to sepsis, there was no effect of external or internal cooling on outcomes [7].

Absence of fever in sepsis is not a good sign

During an infection, fever is elicited by pathogen associated molecular patterns, interacting with immune cells to enhance both the innate and adaptive immune response. As such, the absence of fever in sepsis may reflect a defective immune response, as suggested by lymphopenia and reduced human leukocyte antigen (HLA)-DR monocyte expression in hypothermic sepsis patients. However, this representation is probably oversimplified, as pro-inflammatory cytokine profiles do not differ between febrile and afebrile sepsis patients. Instead, cardiovascular/hemodynamic risk factors may be present in afebrile sepsis patients [13]. Regardless of cause, hypothermic sepsis patients have twice as high mortality rates as those with fever. Whether these patients should be rewarmed, however, is unknown.

Control fever in the patient with brain injury?

Hyperthermia occurs in patients with brain injury even in the absence of infection, often due to neurogenic causes. Induced hypothermia is a practice not supported by evidence. While fever is associated with adverse outcomes following brain injury, fever control is only recommended in one out of three traumatic brain injury guidelines, with no mention in the other two [14] due to the absence of data on the efficacy of fever control in brain injury. In routine care, avoiding extremes of BT is a prudent element of the management of these patients.

Control fever post-cardiac arrest!

In patients after cardiac arrest, preventing fever is a therapeutic measure that is supported both by experimental and clinical studies. To date, however, it is still unclear if hypothermia is more effective than active fever prevention. Per guidelines, fever control should be maintained for the first 72 h after the initial insult in comatose patients following cardiac arrest [15].

Author details
[1] Department of anesthesiology and intensive care unit, North Hospital, Assistance Publique Hôpitaux, service d'anesthésie et de réanimation, hôpital Nord, Chemin des Bourrely, Universitaires de Marseille, Aix Marseille University, 13015 Marseille, France. [2] Centre for Nutrition and Cardiovascular Disease (C2VN), INSERM, INRAE, Aix Marseille University, 13005 Marseille, France. [3] Laboratory of Experimental Intensive Care and Anesthesiology, Amsterdam University Medical Centre Location AMC, Amsterdam, The Netherlands. [4] OLVG Hospital, Amsterdam, The Netherlands. [5] Division of Pulmonary, Critical Care and Sleep Medicine, Department of Internal Medicine, University of New Mexico School of Medicine, Albuquerque, New Mexico, USA. [6] Section of Transfusion Medicine and Therapeutic Pathology, Department of Pathology, University of New Mexico School of Medicine, Albuquerque, New Mexico, USA.

Author contributions
ML, NPJ and NDN conceived the manuscript, assessed the literature and wrote the draft and final version of the manuscript.

Data availability
The authors confirm that the data supporting the findings of this manuscript are available from the referenced manuscripts.

Declarations

Conflicts of interest
ML served as speaker for AOP Pharma and consultant for AOP Pharma, Gilead, LFB, and Viatris. NPJ and NDN have no conflicts of interest to disclose.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 3 February 2023 Accepted: 23 March 2023
Published online: 03 April 2023

References

1. Lefrant JY, Muller L, de La Coussaye JE, Benbabaali M, Lebris C, Zeitoun N, Mari C, Saïssi G, Ripart J, Eledjam JJ (2003) Temperature measurement in intensive care patients: comparison of urinary bladder, oesophageal, rectal, axillary, and inguinal methods versus pulmonary artery core method. Intensive Care Med 29(3):414–418. https://doi.org/10.1007/s00134-002-1619-5
2. O'Grady NP, Barie PS, Bartlett JG, Bleck T, Carroll K, Kalil AC, Linden P, Maki DG, Nierman D, Pasculle W, Masur H, American College of Critical Care Medicine; Infectious Diseases Society of America (2008) Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America. Crit Care Med 36(4):1330–1349. https://doi.org/10.1097/CCM.0b013e318169eda9
3. Lesperance R, Lehman R, Lesperance K, Cronk D, Martin M (2011) Early postoperative fever and the "routine" fever work-up: results of a prospective study. J Surg Res 171(1):245–250. https://doi.org/10.1016/j.jss.2010.03.009
4. Young P, Saxena M, Bellomo R, Freebairn R, Hammond N, van Haren F, Holliday M, Henderson S, Mackle D, McArthur C, McGuinness S, Myburgh J, Weatherall M, Webb S, Beasley R, HEAT Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group (2015) Acetaminophen for fever in critically ill patients with suspected infection. N Engl J Med 373(23):2215–2224. https://doi.org/10.1056/NEJMoa1508375
5. Niven DJ, Laupland KB, Tabah A, Vesin A, Rello J, Koulenti D, Dimopoulos G, de Waele J, Timsit JF, EUROBACT Investigators (2013) Diagnosis and management of temperature abnormality in ICUs: a EUROBACT investigators' survey. Crit Care 17(6):R289. https://doi.org/10.1186/cc13153
6. Hopkins PM, Girard T, Dalay S, Jenkins B, Thacker A, Patteril M, McGrady E (2021) Malignant hyperthermia 2020: Guideline from the Association of Anaesthetists. Anaesthesia 76(5):655–664. https://doi.org/10.1111/anae.15317
7. Schortgen F, Clabault K, Katsahian S, Devaquet J, Mercat A, Deye N, Dellamonica J, Bouadma L, Cook F, Beji O, Brun-Buisson C, Lemaire F, Brochard L (2012) Fever control using external cooling in septic shock: a randomized controlled trial. Am J Respir Crit Care Med 185(10):1088–1095. https://doi.org/10.1164/rccm.201110-1820OC
8. Lee BH, Inui D, Suh GY, Kim JY, Kwon JY, Park J, Tada K, Tanaka K, Ietsugu K, Uehara K, Dote K, Tajimi K, Morita K, Matsuo K, Hoshino K, Hosokawa

K, Lee KH, Lee KM, Takatori M, Nishimura M, Sanui M, Ito M, Egi M, Honda N, Okayama N, Shime N, Tsuruta R, Nogami S, Yoon SH, Fujitani S, Koh SO, Takeda S, Saito S, Hong SJ, Yamamoto T, Yokoyama T, Yamaguchi T, Nishiyama T, Igarashi T, Kakihana Y, Koh Y, Fever and Antipyretic in Critically ill patients Evaluation (FACE) Study Group (2012) Association of body temperature and antipyretic treatments with mortality of critically ill patients with and without sepsis: multi-centered prospective observational study. Crit Care 16(1):R33. https://doi.org/10.1186/cc11211

9. Ye S, Xu D, Zhang C, Li M, Zhang Y (2017) Effect of antipyretic therapy on mortality in critically ill patients with sepsis receiving mechanical ventilation treatment. Can Respir J 2017:3087505. https://doi.org/10.1155/2017/3087505
10. Schell-Chaple HM, Liu KD, Matthay MA, Sessler DI, Puntillo KA (2017) Effects of IV Acetaminophen on core body temperature and hemodynamic responses in febrile critically ill adults: a randomized controlled trial. Crit Care Med 45(7):1199–1207. https://doi.org/10.1097/CCM.0000000000002340
11. Hammond NE, Boyle M (2011) Pharmacological versus non-pharmacological antipyretic treatments in febrile critically ill adult patients: a systematic review and meta-analysis. Aust Crit Care 24(1):4–17. https://doi.org/10.1016/j.aucc.2010.11.002
12. Itenov TS, Johansen ME, Bestle M, Thormar K, Hein L, Gyldensted L, Lindhardt A, Christensen H, Estrup S, Pedersen HP, Harmon M, Soni UK, Perez-Protto S, Wesche N, Skram U, Petersen JA, Mohr T, Waldau T, Poulsen LM, Strange D, Juffermans NP, Sessler DI, Tønnesen E, Møller K, Kristensen DK, Cozzi-Lepri A, Lundgren JD, Jensen JU (2018) Induced hypothermia in patients with septic shock and respiratory failure (CASS): a randomised, controlled, open-label trial. Lancet Respir Med 6(3):183–192. https://doi.org/10.1016/S2213-2600(18)30004-3
13. Wiewel MA, Harmon MB, van Vught LA, Scicluna BP, Hoogendijk AJ, Horn J, Zwinderman AH, Cremer OL, Bonten MJ, Schultz MJ, van der Poll T, Juffermans NP, Wiersinga WJ (2016) Risk factors, host response and outcome of hypothermic sepsis. Crit Care 20(1):328. https://doi.org/10.1186/s13054-016-1510-3
14. Wiles MD, Braganza M, Edwards H, Krause E, Jackson J (2023) Tait F (2023) Management of traumatic brain injury in the non-neurosurgical intensive care unit: a narrative review of current evidence. Anaesthesia. https://doi.org/10.1111/anae.15898
15. Sandroni C, Natalini D, Nolan JP (2022) Temperature control after cardiac arrest. Crit Care 26(1):361. https://doi.org/10.1186/s13054-022-04238-z